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Health and Environmental Effects Profile for 1,2-Dimethylhydrazine

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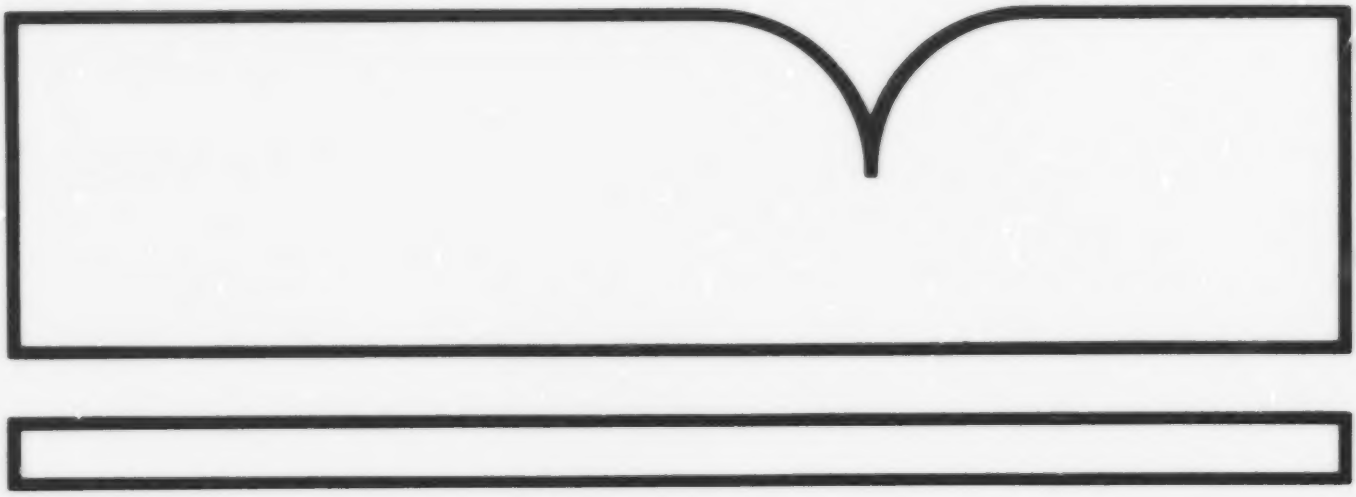

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16. ABSTRACT

The Health and Environmental Effects Profile for 1,2-dimethylhydrazine was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 1,2-Dimethylhydrazine has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for 1,2-dimethylhydrazine is 1.4×10^{3} $(mg/kg\ bw/day)^{-1}$ for oral exposure.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 1,2-DIMETHYLHYDRAZINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

CNS	Central nervous system
DNA	Deoxyribonucleic acid
i.m.	Intramuscular
i.p.	Intraperitoneal
i.v.	Intravenous
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Lethal dose to 50% of recipients
ppm	Parts per million
s.c.	Subcutaneous

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Synonyms for 1,2-dimethylhydrazine include symmetrical dimethylhydrazine, SDMH and N,N'-dimethylhydrazine. 1,2-Dimethylhydrazine will be referred to as 1,2-DMH throughout this profile. The structure of 1,2-DMH is given below:

$$CH_3\text{-}NH\text{-}NH\text{-}CH_3$$

Molecular formula: $C_2H_8N_2$

Molecular weight: 60.1

The Chemical Abstracts Service (CAS) Registry number for 1,2-DMH is 540-73-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1,2-DMH is a clear, colorless, flammable, hygroscopic liquid at ambient temperature (IARC, 1973). It has an ammonia-like fishy smell that is characteristic of alkyl hydrazines. Some of the physical and chemical properties of 1,2-DMH are given below (IARC, 1973, unless otherwise stated):

Boiling point:	80-81°C
Melting point:	-9°C
Specific gravity (20°C):	0.8274
Vapor pressure:	69.9 mmHg at 25°C (NIOSH, 1978) 100 mmHg at 28°C
Solubility:	miscible with water, ethanol, ether, dimethyl formamide and hydrocarbons (IARC, 1973)

1.3. PRODUCTION DATA

Some U.S. producers of laboratory chemicals offer to make small quantities of 1,2-DMH on request for research use, but none produce it in commercial quantities (IARC, 1974). Specific production data were not located in the available literature (see Appendix A). Information is not available on

the method of synthesis used by the laboratory chemical producers, but symmetrical dialkylhydrazines such as 1,2-DMH can be made by reduction of the corresponding azine using lithium aluminum hydride, by hydrolysis of alkylsubstituted diazacyclopropanes, or by reaction of hydrazine with alkyl halides (Raphaelian, 1966).

1.4. USE DATA

There are no known commercial uses for 1,2-DMH. It has been evaluated experimentally as a high-energy propellant, and is used in cancer research to induce tumors in experimental mammals (IARC, 1974).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Information on the environmental fate and transport of 1,2-DMH are not available, presumably due to the limited (i.e., non-commercial) production and use. Structure-reactivity principles (Mill, 1979) can be used, however, to predict the behavior of 1,2-DMH in the environment from information that is available for other hydrazines. Data for hydrazine, methylhydrazine and 1,1-dimethylhydrazine indicate that reaction with ozone and hydroxyl radicals will be the major fate of 1,2-DMH in the atmosphere (Tuazon et al., 1981, 1982; Pitts et al., 1981). Based on kinetic data for these hydrazines, it is expected that the half-lives for reaction of 1,2-DMH with ozone and hydroxyl radical will be on the order of several minutes and several hours, respectively. Photolysis is not expected to occur in the solar actinic region (λ>290 nm) (Tuazon et al., 1981). In water, oxidation of 1,2-DMH by dissolved oxygen is anticipated to be a major pathway for chemical degradation; data for methylhydrazine and 1,1-dimethylhydrazine suggest a half-life on the order of 1 day at neutral or high pH (Banerjee et al., 1977, 1981). Significant volatilization from water at high concentrations may occur (Stauffer, 1977), but volatilization may be less significant at low levels. Upon release to soil, 1,2-DMH is expected to be rapidly oxidized by gaseous or dissolved oxygen, although leaching in areas of high concentrations could occur because the compound is miscible with water.

3. EXPOSURE

Monitoring data for 1,2-DMH in the air, water or food were not found in STORET or the available literature (see Appendix A). The presumed high reactivity of 1,2-DMH suggests that this compound may be rapidly degraded in the environment via chemical pathways and that ambient exposure may be negligible.

4. PHARMACOKINETICS

4.1. ABSORPTION

Marked radioactivity was detected in the blood of rats 15 minutes following the s.c. injection of 21 mg/kg 1,2-di(^{3}H-methyl)hydrazine (Pozharisski et al., 1975). The maximum level of radioactivity was found 3 hours post-injection, after which the level decreased slowly; the level at 24 hours was one-half of the maximum level.

Hydrazine, methylhydrazine and 1,1-dimethylhydrazine are rapidly absorbed in toxic amounts through the skin of dogs (Smith and Clark, 1969, 1971, 1972). NIOSH (1978) has concluded that, in the absence of any other information, it is reasonable to assume that 1,2-DMH also would be absorbed through the skin.

4.2. DISTRIBUTION

1,2-DMH is a potent carcinogen that exhibits a high degree of organ specificity (Section 5.1.). Comprehensive distribution studies have not been conducted, but the specificity appears to be related to dose, route of exposure and tissue metabolism rather than preferential accumulation.

The principal targets of 1,2-DMH carcinogenesis in rodents following chronic low-level exposure in the drinking water include the vascular system, liver and kidneys, but intermittent high level exposure via gavage or injection produce tumors primarily in the large intestine. Acute toxicity studies with rodents and other species exposed via inhalation or injection indicate that effects are primarily manifested in the CNS and liver (Section 5.6.).

4.3. METABOLISM

Druckrey and co-workers postulated that 1,2-DMH is sequentially metabolized *in vivo* to azomethane, azoxymethane, methylazoxymethanol, and ultimately, to methyldiazonium ion and formaldehyde (Druckrey et al., 1967; Preussmann et al., 1969). Methyldiazonium ion is a highly reactive and forms methyl carbonium ion, which presumably initiates carcinogenesis via methylation of macromolecules and other compounds.

Experimental evidence is available to support the above hypothesis. Fiala et al. (1976) administered single s.c. injections of ^{14}C-labeled 1,2-DMH to male F344 rats at dose levels of 21 or 200 mg/kg. At 21 mg/kg, 11% of the administered radioactivity appeared as CO_2 and 14% as azomethane in the exhaled air in 24 hours; the corresponding figures at 200 mg/kg were 4 and 23%, respectively. Expired azomethane was detected almost immediately after injection, and reached 90% of its 24-hour value in 4-5 hours. In a subsequent study, single s.c. injections of 20 mg/kg ^{14}C-azoxymethane were rapidly metabolized by F344 rats to expired $^{14}CO_2$ (25% after 6 hours, 37% after 48 hours), and to ^{14}C-methylazoxymethanol (0.6-1%, 24 hours) which appeared in the urine with other unidentified metabolites (Fiala, 1977). Similar results were obtained by Hawks and Magee (1974); the proportion of dose exhaled as $^{14}CO_2$ within 24 hours following single s.c. injections of 15 mg/kg (mice), 21 mg/kg (rats) or 225 mg/kg (rats) was 24, 13 and 4%, respectively.

In isolated rat liver perfusion experiments (Wolter and Frank, 1982), 1,2-DMH was enzymatically converted to the same metabolites that have been identified *in vivo* (i.e., azomethane, azoxymethane and methylazoxymethanol). *In vitro* hydroxylation of azomethane to methylazoxymetnanol also has been demonstrated with rat liver homogenates and microsomal fractions (Fiala, 1977).

The hypothesis that 1,2-DMH is metabolized via methylazoxymethanol, the proximate carcinogen, is further supported by numerous demonstrations of nucleic acid methylation in the liver and other target tissues (e.g., large intestine, kidney, lung) following in vivo and in vitro exposures (Hawks and Magee, 1974; Pozharisski et al., 1975; Harris et al., 1977; Autrup et al., 1978; Swenberg et al., 1979; Boffa et al., 1982; Bedell et al., 1982).

4.4. EXCRETION

The available metabolism studies indicate that 1,2-DMH and/or metabolites are eliminated rapidly from the body primarily via the kidneys and lungs (see Section 4.3.). When single doses of 15 mg/kg ^{14}C-1,2- DMH were administered by s.c. injection to mice, 10% of the radioactivity was excreted in the urine in 24 hours (Hawks and Magee, 1974).

Less than 1% of a single s.c. 200 mg/kg dose of ^{14}C-1,2-DMH was excreted in the bile of rats as determined by chemical and radioactive assays (Hawks and Magee, 1974). The results of a rat liver perfusion experiment also indicate that biliary excretion is very low (Wolter and Frank, 1982).

5. EFFECTS

5.1. CARCINOGENICITY

1,2-DMH is widely used as a model carcinogen for investigations of the mechanism, histogenesis, prevention and/or therapy of colorectal cancer. Specific areas of study have included effects of dietary components (e.g., fiber, fat), antioxidants (e.g., selenium, vitamin A), age, strain and other modifying influences on the initiation and development of 1,2-DMH-induced carcinogenesis. As indicated in the following summary, extensive evidence is available that demonstrates the induction of cancer in rodents by oral administration or injection of 1,2-DMH.

Chronic administration of low levels of 1,2-dimethylhydrazine dihydrochloride (1,2-DMH dihydrochloride) in the drinking water ($\leq$0.002%) has induced high incidences of vascular system (angiosarcomas) and lung tumors in Swiss mice (Toth and Wilson, 1971; Toth, 1982), and vascular system, liver and cecum tumors in Syrian golden hamsters (Toth, 1972). Exposure of F344 rats to 30 ppm 1,2-DMH in the drinking water for 10 months caused angiosarcomas and hepatocellular carcinomas in the livers (Bedell et al., 1982). In other studies with rats, weekly administration of higher doses of 1,2-DMH (15-30 mg/kg for 5-27 weeks) by gavage has produced high incidences (frequently 80-100%) of malignant intestinal tumors (primarily colon adenocarcinomas) (Druckrey et al., 1967; Druckrey, 1970; Pozharisski, 1972; Rogers and Newberne, 1973; Wilson et al., 1977; Asano and Pollard, 1978; Barbolt and Abraham, 1978; Haller and Milner, 1979; Pollard and Luckert, 1980) and ear canal tumors (Rogers et al., 1973; Wilson et al., 1977). The design and results of the long-term, low-dose drinking water studies are detailed in Tables 5-1 through 5-4.

TABLE 5-1

Summary of Oral Carcinogenicity Study of Toth and Wilson, 1971

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Site	Tumor Type	Tumor Incidence (P value)
Mice/Swiss	M	0.001%[a]	53 weeks[b]	53 weeks[b]	drinking water	vascular system	angiosarcoma[c,d]	46/50
						lung	adenoma[e]	12/50
Mice/Swiss	M	0%	120 weeks[f]	120 weeks[b]	drinking water	vascular system	angiosarcoma	2/110
						lung	adenomas	11/110
Mice/Swiss	F	0.001%[a]	53 weeks[b]	53 weeks[b]	drinking water	vascular system	angiosarcoma[c,g]	49/50
						lung	adenoma[h]	22/50
Mice/Swiss	F	0%	130 weeks[f]	130 weeks[f]	drinking water	vascular system	angiosarcoma	4/110
						lung	adenoma	14/110

[a]Administered as 1,2-DMH dihydrochloride in tap water. The average daily intake of 1,2-DMH dihydrochloride was reported to be 0.087 mg by males and 0.058 mg by females.

[b]Lifetime exposure. Survival was tabulated every 10 weeks of age; no survivors at 60 weeks of age (treatment week 53).

[c]Angiosarcomas were mainly localized in the muscle, liver, pararenal tissues, fat, paraepididymal tissue (males) and parametrial tissue (females).

[d]Average tumor latent period of 42 weeks

[e]Average tumor latent period of 44 weeks (adenoma)

[f]No surviving males at 120 weeks or females at 130 weeks of age.

[g]Average tumor latent period of 45 weeks

[h]Average tumor latent period of 49 weeks (adenoma)

Comments: All organs were examined macroscopically; histologic studies were done on liver, spleen, kidneys, lungs, as well as organs that showed gross pathologic changes. Only a single dose level was tested. As a control, 110 males and 110 females were untreated.

TABLE 5-2

Summary of Oral Carcinogenicity Study of Toth, 1972

Species/ Strain	Sex	Dose or Exposure[a]	Duration of Treatment[b]	Duration of Study[b]	Vehicle or Physical State	Target Site	Tumor Type	Tumor Incidence (P value)
Hamster/ Syrian Golden	M	0.001%	73 weeks	73 weeks	drinking water	vascular system	angiosarcoma	41/50[c]
						cecum	polyploid adenoma	6/50
						liver	benign hepatoma	4/50
							liver cell carcinoma	3/50
Hamster/ Syrian Golden	F	0.001%	73 weeks	73 weeks	drinking water	vascular system	angiosarcoma	44/49[c]
						cecum	polyploid adenoma	8/49
							leiomyosarcoma	3/49
							adenocarcinoma	6/49
						liver	benign hepatoma	7/49
							liver cell carcinoma	3/49

[a]Administered as 1,2-DMH dihydrochloride in tap water. The average daily intake of 1,2-DMH dihydrochloride was reported to be 0.161 mg by males and 0.156 mg by females.

[b]Lifetime exposure. Survival tabulated every 10 weeks of age; no survivors at 80 weeks (treatment week 73).

[c]Average tumor latency period was 45 weeks (males) and 44 weeks (females). The angiosarcomas were mainly localized in the liver, lungs, muscle, heart, and pancreas.

Comments: All organs were examined macroscopically; histologic studies were done on liver, spleen, kidneys, lungs, lymph nodes, as well as organs that showed gross pathologic changes. Control data were not reported and a single dose level was tested.

TABLE 5-3

Summary of Oral Carcinogenicity Study of Toth (1982)

Species/ Strain	Sex[a]	Dose or Exposure[b]	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Site	Tumor Type	Tumor Incidence (P value)
Mice/Swiss	M,F	0.002%	life	life	drinking water	blood vessels lungs	NR NR	79/100 76/100
Mice/Swiss	M,F	0.001%	life	life	drinking water	blood vessels lung	NR	95/100 34/100
Mice/Swiss	M,F	0.0005%	life	life	drinking water	blood vessels lung	NR	91/100 27/100
Mice/Swiss	M,F	0.00025%	life	life	drinking water	blood vessels lung	NR	61/100 16/100
Mice/Swiss	M,F	0.000125%	life	life	drinking water	blood vessels lung	NR	23/100 29/100
Mice/Swiss	M,F	0.0000625%	life	life	drinking water	blood vessels lung	NR	9/100 14/100
Mice/Swiss	M,F	0.00003125%	life	life	drinking water	blood vessels lung	NR	6/100 24/100
Mice/Swiss	M,F	0.000015625%	life	life	drinking water	blood vessels lung	NR	1/100 32/100

[a]50 mice/sex/dose were treated

[b]Administered as 1,2-DMH dihydrochloride

NR = Not reported

Comments: These data were published in an abstract. The induction of blood vessel tumors is dose-related when the highest dose (which was toxic) is excluded. Incidence of tumors in untreated mice was not reported.

TABLE 5-4

Summary of Oral Carcinogenicity Study of Bedell et al. (1982)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
Rats/F344	M	30 ppm*	10 months	10 months	drinking water	liver	angiosarcomas	14/15
							hepatocellular carcinoma	6/15
						lung	metastatic angiosarcomas	7/15
						kidney	cortical adenoma	1/15
							early mesenchymal	2/15

*Administered as 85 ppm 1,2-DMH dihydrochloride. Water consumption data indicated that the rats consumed 1.7-2.4 mg 1,2-DMH/kg/day.

Comments: Control data were not reported; this was a limited study that was designed to demonstrate a correlation between the ability to repair O^6-methylguanine and cell specificity for carcinogenesis. Complete necropsies and histopathologic evaluations of all gross lesions, liver, lung and kidneys were performed.

Numerous studies have shown that 1,2-DMH is a potent colorectal carcinogen when administered by s.c. injection to mice (e.g., IARC, 1974; Thurnherr et al., 1973; Richards, 1977; Barthold and Beck, 1980; Diwan and Blackman, 1980; Szakal et al., 1980; Turusov, 1980; Glauert et al., 1979, 1981; London et al., 1981; Martin et al., 1981; Clapp et al., 1981; Schattenkerk et al., 1981; Turusov et al., 1982; Corasanti et al., 1982; Kumagai et al., 1982), rats (e.g., IARC, 1974; Martin et al., 1973; Reddy et al., 1974; Fukushima et al., 1977; Jacobs, 1977; Bauer et al., 1979; Castleden and Shilkin, 1979; Roussel et al., 1980; Freeman et al., 1980; Harte et al., 1981; Jacobs et al., 1981; Tempero et al., 1981; Celik et al., 1981; Heitman and Cameron, 1982; Ankerst and Sjoegren, 1982; Koga et al., 1982) and hamsters (Martin et al., 1981). Subcutaneous administration appears to be the most reliable route of exposure for the induction of colonic cancer. In these studies 1,2-DMH was typically administered as single weekly doses of 10-30 mg/kg, and high incidences (generally ranging from 40-100%, depending on rodent strain) of colon and rectum tumors developed after 10-30 weeks of treatment. Reduced s.c. injection schedules were also carcinogenic; six weekly inoculations of 20 mg/kg 1,2-DMH produced colon neoplasms in 83% of treated and 0% of control CF_1 female mice after 14-39 weeks of latency (Deschner and Long, 1977), and single s.c. injections of 150-200 mg/kg have produced intestinal tumors in rats (Reddy et al., 1977). Weekly 20-30 mg/kg i.p. injections in rats (Rubio et al., 1980), thrice weekly 250 mg/kg intrarectal doses in rats (Markert et al., 1978), and 34 weekly 4.3 mg/kg i.m. injections in hamsters (Osswald and Kruger, 1969) also produced elevated incidences of intestinal adenocarcinomas. Extracolonic tumors resulting from standard s.c. administration of 1,2-DMH (as described above) have been

observed in the kidneys, ear ducts, pancreas and Zymbal gland of rats (Reddy et al., 1975; Sunter and Senior, 1982) and clitoral glands of mice (Turusov, 1980).

The carcinogenicity of 1,2-DMH in animals is further supported by evidence that azoxymethane, a presumed metabolite, produced intestinal carcinomas and liver tumors in rats and mice when given orally or by s.c., i.p. or i.m. injection (Preussmann et al., 1969; Gennaro et al., 1973). Also, a single i.v. injection of azoxymethane during gestation reportedly produced renal and neurogenic tumors in the offspring of rats (Druckrey, 1973).

5.2. MUTAGENICITY

Largely because it is an alkylating agent and an unequivocal animal carcinogen, 1,2-DMH has been tested extensively for mutagenicity (particularly in validation studies and studies of interactions with DNA and its constituents). Mutagenicity studies of 1,2-DMH are summarized in Table 5-5. The overall weight of evidence from a battery of microbial and mammalian tests indicates that 1,2-DMH should be regarded as a promutagen and that negative responses can be attributed to ineffective exposures and/or unresponsive strains or species of indicator organism.

Negative mutagenic responses were generally elicited in Salmonella/Ames assays with and without S-9 metabolic activation (see Table 5-5). The positive results of Parodi et al. (1981) suggest, however, that the bacteria in the other studies may have been exposed to insufficient concentrations of 1,2-DMH; the Parodi et al. (1981) plate incorporation and spot assays used the highest levels of 1,2-DMH. Host-mediated assays with mice elicited reversions to histidine independence in S. typhimurium strains G46, TA1530 and TA1950 (Moriya et al., 1978; Simmon, 1979; Von Wright and Tikkanen,

TABLE 5-5

Mutagenicity Testing of 1,2-Dimethylhydrazine

Assay	Indicator Organism	Concentration or Dose	Application	Activation System	Response	Reference
Reverse mutation (his^+)	S. typhimurium G46, TA1350, TA1535	$<2.5 \times 10^2$ µmol/mt	liquid incubation	+	-	Bartsch et al., 1980
Reverse mutation (his^+)	S. typhimurium G46, TA1530, TA1535	$<1.4 \times 10^2$ µmol/plate	plate incorporation	+	-	Bartsch et al., 1980
Reverse mutation (his^+)	S. typhimurium TA1535, TA1536, TA1537, TA1538, TA98, TA100	<4.2 µmol/plate	plate incorporation	±	-	Simmon, 1979
Reverse mutation (his^+)	S. typhimurium TA1535, TA1538	4.2 µmol/plate	plate incorporation	±	-	Rosenkranz and Poirier, 1979
Reverse mutation (his^+)	S. typhimurium TA100	16.7 µmol/disc	spot test	NR	+	Parodi et al., 1981
Reverse mutation (his^+)	S. typhimurium TA100	9.4-150 µmol/plate	plate incorporation	±	±	Parodi et al., 1981
Reverse mutation (his^+)	S. typhimurium TA100	NR	liquid incubation	+	+	Parodi et al., 1981
Reverse mutation (his^+)	S. typhimurium TA100	1.0-50.0 µmol/plate	plate incorporation	±	-	Von Wright and Tikkanen, 1980
Reverse mutation (his^+) (host-mediated)	S. typhimurium TA1950	100 mg/kg, oral administration	bacteria injected i.p. into mice	NA	+	Von Wright and Tikkanen, 1980
Reverse mutation (his^+) (host-mediated)	S. typhimurium G46	10-50 mg/kg, single oral dose	bacteria injected i.p. into mice	NA	+	Moriya et al., 1978
Reverse mutation (his^+) (host-mediated)	S. typhimurium TA1530	125 mg/kg, i.m. injection	bacteria injected i.p. into mice	NA	±	Simmon, 1979
Reverse mutation (his^+) (host-mediated)	S. typhimurium TA1538	125 mg/kg, i.m. injection	bacteria injected i.p. into mice	NA	-	Simmon, 1979
Reverse mutation (his^+) (host-mediated)	S. typhimurium TA1535	995 mg/kg, oral administration	bacteria injected i.p. into mice	NA	-	Simmon, 1979

TABLE 5-5 (cont.)

Assay	Indicator Organism	Concentration or Dose	Application	Activation System	Response	Reference
Reverse mutation (tryp$^+$)	E. coli WP2	0.5-2.0 µmol/plate	plate incorporation	-	-	Von Wright and Tikkanen, 1980
Reverse mutation (tryp$^+$)	E. coli WP2	0.5-2.0 µmol/disc	spot test	-	-	Von Wright and Tikkanen, 1980
Reverse mutation (his$^+$ and Met$^+$)	B. subtilis TKJ6321	0.08-5.0 µmol/plate	plate incorporation	+	+[a] +	Felkner et al., 1979
Growth inhibition (DNA repair)	B. subtilis rec$^-$/rec$^+$ strains[c]	serial dilutions from limit of solubility	plate incorporation spot test	+ +	o[b] +	Suter and Jaeger, 1982
Growth inhibition (DNA repair)	E. coli rec$^-$/rec$^+$ strains[d]	serial dilutions from limit of solubility	plate incorporation spot test	+ +	o[b] +	Suter and Jaeger, 1982
Growth inhibition (DNA repair)	E. coli pol A$^+$/pol A$^-$	250 µl/disc	spot test	+	+	Rosenkranz and Poirier, 1979
Growth inhibition (DNA repair)	B. subtilis rec$^-$ and/or exc$^-$ strains[e]	50 µl/disc	spot test	-	+[a]	Felkner et al., 1979
Mitotic recombination	S. cerevisiae D3	doses giving 55-100% survival	NR	-	+	Zimmerman and Schwaier, 1967
Mitotic recombination	S. cerevisiae D4	2.5%	liquid suspension	+	-	Simmon et al., 1979
Mitotic recombination (host-mediated)	S. cerevisiae D4	995 mg/kg, oral administration	bacteria injected i.p. into mice	NA	-	Simmon et al., 1979
Forward mutation (TK)	mouse lymphoma cells (L5178Y)	0.1-5.0 mM	in vitro culture	NA	+	Rogers and Back, 1981
Forward mutation (IdR, TC or Ara-C)	mouse lymphoma cells (L5178Y)	0.1-5.0 mM	in vitro culture	NA	-	Rogers and Back, 1981
Inhibition of testicular DNA synthesis	mice	200 mg/kg	single oral dose	NA	+	Seiler, 1977

TABLE 5-5 (cont.)

Assay	Indicator Organism	Concentration or Dose	Application	Activation System	Response	Reference
Unscheduled DNA synthesis	rats, F344/CrlBr hepatocytes	3 mg/kg/day	oral x 1.5-16 days oral x 28 days	NA NA	+ -	Lewis and Swenberg, 1982
DNA fragmentation (alkaline elution)	BALB/c mice, liver, lung, kidney, stomach, colon	200 mg/kg[f]	oral or s.c.	NA	+	Brambilla et al., 1978
DNA fragmentation (alkaline elution)	Swiss mice, liver and lungs	190 mg/kg[f] 32 mg/kg/day[f]	single i.p. injection i.p. injection x 5 days	NA NA	+ +	Parodi et al., 1981
Sister chromatid exchange	Chinese hamster ovary cells	$\geq 10^{-5}$ M	in vitro culture	NA	+	MacRae and Stich, 1979
Micronucleus	rats, Sprague-Dawley bone marrow cells	20-200 mg/kg	single i.p. injection	NA	-	Irzos et al., 1978

[a]Optimum response was found at pH 6.5.

[b]With the exception of a negative response with B. subtilis HLL3g/HJ-15 and a positive response with E. coli AB1157/HJ-15, bacteriotoxicity precluded assessment of DNA damage.

[c]B. subtilis strains H17/M45 and HLL3g/HJ-15 were tested.

[d]E. coli strains AB1157/JC5547, AB1157/JC2921, AB1157/JC2926 and AB1157/JC5519 were tested.

[e]Lethal DNA damage was detected in rec$^-$ strains rec A0, rec E4, and MC-1; exc$^-$ strain hcr-9, and rec$^-$, exc$^-$ strain fh2006-2007. Damage was not induced in recA1, recB2, recC5, recD3 or recG13. All of the repair-deficient strains are isogenic with the repair-intact (wild type) B. subtilis strain 168.

[f]1,2-Dimethylhydrazine·2HCl

NA = Not available; NR = Not reported

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1980), but not in strains TA1535 or TA1538 (Simmon et al., 1979). Reverse mutation tests using E. coli WP2 tryptophan auxotroph were negative without activation (Von Wright and Tikkanen, 1980) but similar tests with B. subtilis TKJ6321 (a histidine and methionine auxotroph) with or without metabolic activation were positive (Felkner et al., 1979). Differential growth inhibition was observed with wild type and DNA repair deficient (rec^-, $polA^-$) strains of B. subtilis (Felkner et al., 1979; Suter and Jaeger, 1982) and E. coli (Rosenkranz and Poirier, 1979; Suter and Jaeger, 1982), indicating lethal or mutagenic interaction of 1,2-DMH with DNA. In tests with yeast, 1,2-DMH induced mitotic recombination in S. cerevisiae D3 (Zimmerman and Schwaier, 1967) but not in strain D4 when tested in liquid suspension or host-mediated assays (Simmon, 1979; Simmon et al., 1979).

In mutagenesis assays with cultured mouse lymphoma (L5178y) cells, 1,2-DMH caused forward mutation to thymidine resistance but not to ouabain, thioguanine or cytosine arabinoside resistance (Rogers and Back, 1981). In vivo exposure to 1,2-DMH inhibited testicular DNA synthesis in mice (Seiler, 1977), induced unscheduled DNA synthesis in rat hepatocytes (Lewis and Swenberg, 1982) and caused DNA fragmentation in various tissues of mice (Brambilla et al., 1978; Parodi et al., 1981). In vitro treatment with 1,2-DMH induced sister chromatid exchanges in cultured Chinese hamster ovary cells (MacRae and Stich, 1979), but exposure of rats to 1,2-DMH did not produce micronuclei in the bone marrow cells; additional cytogenetic tests with 1,2-DMH have not been conducted.

5.3. TERATOGENICITY

Druckrey (1973) has noted that 1,2-DMH was not teratogenic in BD rats, but additional detail regarding this finding was not reported.

Teratogenic effects were observed in South African clawed toad larvae, Xenopus laevis, following continuous embryonic exposure to 1,2-DMH concentrations of 50 or 80 mg/ℓ (Greenhouse, 1976a). 1,2-DMH was teratogenic during the neurulation period of embryogenesis, producing malformations of the head, trunk and tail; the most frequent malformation was tail kinks. The relevance of these findings to mammals is unclear since a non-placental species was used and the embryos were directly (externally) exposed to the chemical.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of 1,2-DMH were not located in the available literature.

5.5. CHRONIC TOXICITY

The chronic oral studies of 1,2-DMH (see Section 5.1.) were designed for evaluation of carcinogenicity, and did not detail non-neoplastic effects of exposure.

Weekly intragastric administration of 1,2-DMH to guinea pigs (30 mg/kg/week x 10 weeks, 60 mg/kg/week x 7 weeks) or dogs (5 mg/kg/week x 10 weeks, 15 mg/kg/week x 8 weeks, 30 or 60 mg/kg x 2 weeks) was hepatotoxic (degeneration, hemorrhagic necrosis) but not tumorigenic (Wilson, 1976). Similar treatment of miniature swine (30 or 60 mg/kg/week x 10 weeks) produced hepatomas and bile duct carcinomas, but treatment of rats (30 mg/kg/week x 8 weeks) was not hepatotoxic. Weekly s.c. injections of 1,2-DMH in the same range of doses and frequencies were similarly hepatotoxic to guinea pigs, dogs and miniature swine.

5.6. OTHER RELEVANT INFORMATION

An inhalation exposure of 280-400 ppm for 4 hours has been reported to be an LC_{50} for rats (Jacobson et al., 1955). For guinea pigs, an LD_{50} for skin absorption was reported to be 131 mg/kg (Rothberg and Cope, 1955). The primary effects of acute inhalation exposure in rats, mice and dogs is CNS dysfunction (e.g., respiratory difficulties and convulsions) (Jacobson et al., 1955). Single i.p. injections of 1,2-DMH in the lethal dose range were hepatotoxic to rats (495 mg/kg) and mice (54-77 mg/kg) (Weir et al., 1965).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Pertinent data regarding the acute toxicity of 1,2-DMH in fish species were not located in the available literature.

In a series of papers, Greenhouse (1975, 1976a,b) reported on the toxicity and teratogenic effects of 1,2-DMH on embryo and larval stages of the South African clawed toad, Xenopus laevis. Concentrations of 0, 10, 20, 40, 50 and 80 mg 1,2-DMH/ℓ were used to determine an effective teratogenic level. Malformed embryos were 3, 4, 4, 5, 100 and 100%, respectively, at the dose levels tested in groups of 100 embryos (Greenhouse, 1976a). Embryo abnormalities included failure to elongate and tail kinks. Of the larvae exposed to 1.0 (n=62) and 10.0 mg/ℓ (n=5), none survived (0% survival) for a period of 120 hours, while larvae exposed at 0.1 (n=5) and controls (n=65) had 100% survival at 120 hours (Greenhouse, 1976b). Larvae exposed continuously to 0.1 mg/ℓ throughout their development survived and metamorphosed normally.

6.2. CHRONIC TOXICITY

Pertinent data regarding the effects of chronic exposure to 1,2-DMH in aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

The effect of 1,2-DMH on the alga, Selenastrum capricornutum, was tested by Scherfig and Dixon (1975). Although quantitative data on the inhibition of cell growth were not available, 1,2-DMH was reported to be less toxic than hydrazine or monomethylhydrazine.

6.4. RESIDUES

Pertinent data regarding residues of 1,2-DMH in aquatic organisms were not located in the available literature. However, its miscibility with water indicates that the bioconcentration potential of 1,2-DMH is very low or nil, since log BCF is inversely related to the log of water solubility (Kenaga and Goring, 1980).

6.5. OTHER RELEVANT INFORMATION

Additional information relevant to the aquatic toxicity of 1,2-DMH was not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Recommended or promulgated occupational or environmental exposure limits for 1,2-DMH were not located in the available literature. NIOSH (1978) recognizes 1,2-DMH as an occupational carcinogen, but has not recommended a limit because an acceptable method of sampling and analysis is presently unavailable.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 1,2-DMH were not located in the available literature.

8. RISK ASSESSMENT

1,2-DMH is a potent animal carcinogen that exhibits a high degree of organ specificity depending upon the dose and route of administration. When administered continuously at relatively low doses in the drinking water, vascular system, liver and/or lung tumors were induced in mice, hamsters and rats (Toth and Wilson, 1971; Toth, 1972, 1982; Bedell et al., 1982). When administered intermittently at high doses by weekly gavage or s.c. injection to rodents, the large intestine is the principal target for 1,2-DMH carcinogenesis (see Section 5.1.). The high incidence of tumors at sites other than the colon in the drinking water studies may be related to the factors that chemicals administered via s.c. injection avoid direct passage through the liver, and that different metabolic pathways may be available when a low dose is given slowly but continuously.

The data for the angiosarcoma response of female mice (Toth and Wilson, 1971) can be used to derive a carcinogenic potency factor (q_1^*) for 1,2-DMH. In this study, 1,2-DMH dihydrochloride was administered to the mice. Although it is not absolutely clear how the quantitative risk associated with the ingestion of the dihydrochloride is related to 1,2-DMH, since absorption as well as other biochemical and pharmacological properties may vary between the two compounds, the use of this study is justified because ingested 1,2-DMH may be protonated to form the dihydrochloride in the stomach acid. Further, it is likely that the free base or hydrochloride forms would not elicit different toxicologic responses at the low doses used because the buffering capacity in the digestive tract would determine the form of 1,2-DMH. The incompletely reported results of the Toth (1982) study are supportive because they show that the induction of blood vessel tumors

in mice is related to the concentration of 1,2-DMH in drinking water (eight concentrations were tested), but these data cannot be used for quantitative risk estimation because control data were not reported.

Based on the angiosarcoma data for female mice (Toth and Wilson, 1971) and using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980), a q_1^* of 1.38×10^3 $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 7.25×10^{-9} mg/kg/day or 5.08×10^{-7} mg/day for a 70 kg man. Complete data for derivation of the q_1^* are presented in Appendix B.

9. REFERENCES

Ankerst, J. and H.O. Sjoegren. 1982. Effect of selenium on the induction of breast fibroadenomas by adenovirus type 9 and 1,2-dimethylhydrazine-induced bowel carcinogenesis in rats. Int. J. Cancer. 29(6): 707-710.

Asano, T. and M. Pollard. 1978. Strain susceptibility and resistance to 1,2-dimethylhydrazine-induced enteric tumors in germfree rats. Proc. Soc. Exp. Biol. Med. 158(1): 89-91.

Autrup, H., G.D. Stoner, F. Jackson, et al. 1978. Explant culture of rat colon: A model system for studying metabolism of chemical carcinogens. In Vitro. 14(10): 868-877.

Banerjee, S., H.C. Sikka and R. Gray. 1977. Environmental Degradation of 1,1-Dimethylhydrazine. Proc. Conf. Environ. Chem. Hydrazine Fuels, Tyndall AFB. p. 113-128. NTIS AD-A054194.

Banerjee, S., E.J. Pack, Jr., H. Sikka and C.M. Kelly. 1981. Kinetics of oxidation of methylhydrazines in water factors controlling the formation of 1,1-dimethylnitrosamine from the corresponding hydrazine. Unpublished study conducted at Syracuse Research Corporation.

Barbolt, T.A. and R. Abraham. 1978. The effect of bran on dimethyhydrazine-induced colon carcinogenesis in the rat. Proc. Soc. Exp. Pathol. Toxicol. 157(4): 656-659.

Barthold, S.W. and D. Beck. 1980. Modification of early dimethylhydrazine carcinogens by colonic mucosal hyperplasia. Cancer Res. 40(12): 4451-4455.

Bartsch, H., C. Malaveille, A.M. Camus, et al. 1980. Validation and comparative studies on 180 chemicals with S. typhimurium strains and V79 Chinese hamster cells in the presence of various metabolizing systems. Mutat. Res. 76: 1-50.

Bauer, H.G., N.G. Asp, R. Oste, A. Dahlqvist and P.E. Fredlund. 1979. Effect of dietary fiber on the induction of colorectal tumors and fecal beta-glucuronidase activity in the rat. Cancer Res. 39(9): 3752-3756.

Bedell, M.A., J.G. Lewis, K.C. Billings and J.A. Swenberg. 1982. Cell specificity in hepatocarcinogenesis -- Preferential accumulation of O-6-methylguanine in target-cell DNA during continuous exposure of rats to 1,2-dimethylhydrazine. Cancer Res. 42(8): 3079-3083.

Boffa, L.C., R.J. Gruss and V.G. Allfrey. 1982. Aberrant and nonrandom methylation of chromosomal DNA-binding proteins of colonic epithelial-cells by 1,2-dimethylhydrazine. Cancer Res. 42(2): 382-388.

Brambilla, G., M. Cavanna, S. Parodi, L. Sciaba, A. Pino and L. Robbiano. 1978. DNA damage in liver, colon, stomach, lung and kidney of BALB/c mice treated with 1,2-dimethylhydrazine. Int. J. Cancer. 22(2): 174-180.

Castleden, W.M. and K.B. Shilkin. 1979. Diet, liver function and dimethyl-hydrazine-induced gastrointestinal tumors in male Wistar rats. Br. J. Cancer. 39(6): 731-739.

Celik, C., A. Mittleman, N.S. Paolin, D. Lewis and J.T. Evans. 1981. Effects of 1,2-symmetrical dimethylhydrazine on Jejunocolic transposition in Sprague-Dawley rats. Cancer Res. 41: 2908-2911.

Clapp, N.K., J.F. London, M.A. Henke and T.L. Shock. 1981. Enhancement by dietary brans of 1,2-dimethylhydrazine colon carcinogenesis in male BALB-c mice. Proc. Am. Assoc. Cancer Res. 22: 114.

Corasanti, J.G., G.H. Hobika and G. Markus. 1982. Interference with dimethylhydrazine induction of colon tumors in mice by epsilon-aminocaproic acid. Science. 216(4549): 1020-1021.

Deschner, E.E. and F.C. Long. 1977. Colonic neoplasms in mice produced with six injections of 1,2-dimethylhydrazine. Oncology. 34(6): 255-257.

Diwan, B.A. and K.E. Blackman. 1980. Differential susceptibility of 3 sublines of C57BL-6 mice to the induction of colorectal tumors by 1,2-dimethylhydrazine. Cancer Lett. 9(2): 111-116.

Druckrey, H. 1970. Production of colonic carcinomas by 1,2-dialkylhydrazines and azoxyalkanes. In: Carcinomas of the Colon and Antecedent Epithelium, W.J. Burdette, Ed. Thomas, Springfield, IL. p. 267. (Summarized in IARC, 1974)

Druckrey, H. 1973. Specific carcinogenic and teratogenic effect of indirect alkylating methyl and ethyl compounds, and their dependency on stages of ontogenic development. Xenobiotica. 3: 271-303.

Druckrey, H., R. Preussman, F. Matzkies and S. Ivankovic. 1967. Selektive Erzeugung von Darmkrebs bei Ratten durch 1,2-Dimethylhydrazin. Naturwissenschaften. (Ger.) 54: 285-286. (Cited in IARC, 1974; Fiala, 1977)

Felkner, I.C., K.M. Hoffman and B.C. Wells. 1979. DNA-damaging and mutagenic effects of 1,2-dimethylhydrazine on Bacillus subtilis repair-deficient mutants. Mutat. Res. 68: 31-40.

Fiala, E.S. 1977. Investigations into the metabolism and mode of action of the colon carcinogens 1,2-dimethylhydrazine and azoxymethane. Cancer. 40(5): 2436-2445.

Fiala, E.S., C. Kulakis, G. Bobotas and J.H. Weisburger. 1976. Brief communication: Detection and estimation of azomethane in expired air of 1,2-dimethylhydrazine-treated rats. J. Natl. Cancer Inst. 56:1271-1273.

Freeman, H.J., G.A. Spiller and Y.S. Kim. 1980. A double-bind study on the effects of differing purified cellulose and pectin fiber diets on 1,2-dimethylhydrazine-induced rat colonic neoplasia. Cancer Res. 40: 2661-2665.

Fukushima, S., T. Hibino, M. Shibata, G. Murasaki, T. Ogiso and N. Ito. 1977. Effect of hepatotoxic or nephrotoxic agents on the induction of colon cancers in rats by 1,2-dimethylhydrazine. Toxicol. Appl. Pharmacol. 40(3): 561-570.

Gennaro, A.R., R. Villanueva, Y. Sukonthaman, V. Vathanophas and G.P. Rosemond. 1973. Chemical carcinogenesis in transposed intestinal segments. Cancer Res. 33: 536. (Summarized in IARC, 1974)

Glauert, H.P., C.H. Sander, V.L. Sanger and M.R. Bennink. 1979. Influence of dietary agar and tallow on colon carcinogenesis. Fed. Proc. 38(3): 714.

Glauert, H.P., M.R. Bennink and C.H. Sander. 1981. Enhancement of 1,2-dimethylhydrazine-induced colon carcinogenesis in mice by dietary agar. Food Cosmet. Toxicol. 19(3): 281-286.

Greenhouse, G.A. 1975. Effects of pollutants on embryos and larvae of frogs: A system for evaluating teratogenic effects of compounds in freshwater environments. Aerosp. Med. Res. Lab. No. AMRL-TR-125. p. 493-511.

Greenhouse, G. 1976a. Evaluation of teratogenic effects of hydrazine, methylhydrazine and dimethylhydrazine on embryos of Xenopus laevis, the South African clawed toad. Teratology. 13: 167-177.

Greenhouse, G. 1976b. The evaluation of the toxic effects of chemicals in freshwater by using frog embryos and larvae. Environ. Pollut. 11(4): 303-315.

Haller, J.K. and J.A. Milner. 1979. Effect of refined carbohydrates on colon cancer in the albino rat. Fed. Proc. 38(3): 714.

Harris, C.C., H. Autrup, G.D. Stoner, E.M. McDowell, B.F. Trump and P. Schafer. 1977. Metabolism of dimethylnitrosamine and 1,2-dimethylhydrazine in cultured human bronchi. Cancer Res. 37(7): 2309-2311.

Harte, P.J., G. Steele, Jr., A.A. Rayner, A.E. Munroe, V.P. King and R.E. Wilson. 1981. Effect of major small bowel resection on dimethylhydrazine-induced bowel carcinogenesis. J. Surg. Oncol. 18(1): 87-94.

Hawks, A. and P.N. Magee. 1974. The alkylation of nucleic acids of rat and mouse *in vivo* by the carcinogen 1,2-dimethylhydrazine. Br. J. Cancer. 30: 440.

Heitman, D.W. and I.L. Cameron. 1982. Effects of dimethylhydrazine treatment and feeding regimen on cell-proliferation in the rat descending colon. Proc. Am. Assoc. Cancer Res. 23: 69.

IARC (International Agency for Research on Cancer). 1973. 1,2-Dimethylhydrazine. *In*: Some Aromatic Amines, Hydrazine and Related Substances. N-Nitrosocompounds and Miscellaneous Alkylating Agents. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. IARC, WHO, Lyon, France. Vol. 4, p. 145-152.

Jacobs, M.M. 1977. Inhibitory effects of selenium on 1,2-dimethylhydrazine and methylazoxymethanol colon carcinogenesis. Correlative studies on selenium effects on the mutagenicity and sister chromatid exchange rates of selected carcinogens. Cancer. 40(5): 2557-2564.

Jacobs, M.M., C.F. Forst and F.A. Beams. 1981. Biochemical and clinical effects of selenium on dimethylhydrazine-induced colon cancer in rats. Cancer Res. 41(11): 4458-4465.

Jacobson, K.H , J.H. Clem, H.J. Rinehart and N. Mayes. 1955. The acute toxicity of the vapors of some methylated hydrazine derivatives. AMA Arch. Ind. Health. 12: 609-676.

Kenaga, E.E. and C.A.I. Goring. 1980. Relationship between water solubility, soil sorption, octanol-water partitioning, and concentration of chemicals in biota. In: Aquatic Toxicology - ASTM STP 707, J.G. Eaton, P.R. Parrish and A.C. Hendricks, Ed. Amer. Soc. Test. Mater. Philadelphia, PA: 78-115.

Koga, S., N. Kaibara and R. Takeda. 1982. Effect of bile acids on 1,2-dimethylhydrazine-induced colon cancer in rats. Cancer. 50(3): 543-547.

Kumagai, J., A. Kawaura, K. Furuya, K. Izumi and H. Otsuka. 1982. Perianal lesions of BALB/c mice induced by 1,2-dimethylhydrazine dihydrochloride and methylazoxymethanol acetate: Their classification and histogenesis. Gann. 73(3): 358-364.

Lewis, J.G. and J.A. Swenberg. 1982. Effect of 1,2-dimethylhydrazine and diethylnitrosamine on cell replication and unscheduled DNA-synthesis in target and non-target cell-populations in rat liver following chronic administration. Cancer Res. 42(1): 89-92.

London, J.F., N.K. Clapp and M.A. Henke. 1981. Effects of dietary bran and the colon carcinogen 1,2-dimethylhydrazine on fecal beta-glucuronidase activity in mice. Food Cosmet. Toxicol. 19(6): 707-711.

MacRae, W.D. and H.F. Stich. 1979. Induction of sister-chromatid exchanges in Chinese hamster ovary cells by thiol and hydrazine compounds. Mutat. Res. 68(4): 351-366.

Markert, C., L.W. Rogers and J.F. Chiu. 1978. Induction of colonic adenocarcinomas by 1,2-dimethylhydrazine intrarectally administered in rats. Digestion. 18(3-4): 261-265.

Martin, F., R. Michiels, H. Bastien, E. Justrabo, M. Bordes and B. Viry. 1973. An experimental model for cancer of the colon and rectum. Digestion. 8: 22. (Summarized in IARC, 1973)

Martin, M.S., E. Justrabo, J.F. Jeannin, A. Leclerc and F. Martin. 1981. Effect of dietary chenodeoxycholic acid on intestinal carcinogenesis induced by 1,2-dimethylhydrazine in mice and hamsters. Br. J. Cancer. 43(6): 884-886.

Mill, T. 1979. Structure Reactivity Correlation for Environmental Reactions. EPA 560/11-79-012.

Moriya, M., T. Kato, K. Watanabe, Y. Wantanabe and Y. Shirasu. 1978. Detection of mutagenicity of the colon carcinogen 1,2-dimethylhydrazine by the host-mediated assay and its correlation to carcinogenicity. J. Natl. Cancer Inst. 61: 457-460.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard...Occupational Exposure to Hydrazines. DHEW(NIOSH) Publ. No. 78-172. U.S. DHEW, PHS, CCD, NIOSH, Cincinnati, OH. 269 p.

Osswald, H. and F.W. Kruger. 1969. Die cancerogene Wirkung von 1,2-dimethylhydrazin beim Goldhamster. Arzneimittel-Forsch. (Ger.) 19: 1891. (Summarized in IARC, 1974)

Parodi, S., S. DeFlora, M. Cavanna, et al. 1981. DNA damaging activity in vivo and bacterial mutagenicity of sixteen hydrazine derivatives as related quantitatively to their carcinogenicity. Cancer Res. 41: 1469-1482.

Pitts, J.H., Jr., E.C. Tuazon, W.P.L. Carter, et al. 1981. Atmospheric Chemistry of Hydrazines: Gas Phase Kinetics and Mechanistic Studies. Report prepared by the Statewide Air Pollution Research Center, University of California, Riverside, CA, for the Air Force Engineering and Services Center, Tyndall AFB, FL. NTIS AD-A093486.

Pollard, M. and P.H. Luckert. 1980. Indomethacin treatment of rats with dimethylhydrazine-induced intestinal tumors. Cancer Treat. Rep. 64(12): 1323-1328.

Pozharisski, K.M. 1972. Intestinal tumours induced in rats with 1,2-dimethylhydrazine. Vop. Onkol. 18: 64. (Summarized in IARC, 1973)

Pozharisski, K.M., Yu M. Kapustin, A.J. Linhacheu and J.D. Shaposhnikov. 1975. The mechanism of carcinogenic action of 1,2-dimethylhydrazine (SDMH) in rats. Int. J. Cancer. 15: 673-683.

Preussmann, R., H. Druckrey, S. Ivankovic and A. von Hodenberg. 1969. Chemical structure and carcinogenicity of aliphatic hydrazo, azo and azoxy compounds and of triazenes, potential in vivo alkylating agents. Ann. NY Acad. Sci. 163: 697.

Raphaelian, L.A. 1966. Hydrazine. In: Encyclopedia of Chemical Technology, 2nd ed., Vol. 11, R.E. Kirk and D.F. Othmer, Ed. John Wiley and Sons, Inc., NY. p. 164. (Cited in IARC, 1974)

Reddy, B.S., J.H. Weisburger, T. Narisawa and E.L. Wynder. 1974. Colon carcinogenesis in germ-free rats with 1,2-dimethylhydrazine and N-methyl-N'-nitro-N-nitrosoguanidine. Cancer Res. 34(9): 2368-2372.

Reddy, B.S., T. Narisawa, P. Wright, D. Vukusich, J.H. Weisburger and E.L. Wynder. 1975. Colon carcinogenesis with azoxymethane and dimethylhydrazine in germ-free rats. Cancer Res. 35(2): 287-290.

Reddy, B.S., K. Watanabe and J.H. Weisburger. 1977. Effect of high-fat diet on colon carcinogenesis in F-344 rats treated with 1,2-dimethylhydrazine, methylazoxymethanol acetate or methylnitrosourea. Cancer Res. 37(11): 4156-4159.

Richards, T.C. 1977. Early changes in the dynamics of crypt cell populations in mouse colon following administration of 1,2-dimethylhydrazine. Cancer Res. 37(6): 1680-1685.

Rogers, A.E. and P.M. Newberne. 1973. Dietary enhancement of intestinal carcinogenesis by dimethylhydrazine in rats. Nature. 246: 491-492.

Rogers, A.E., B.J. Herndon and P.M. Newberne. 1973. Induction by dimethylhydrazine of intestinal carcinoma in normal rats and rats fed high or low levels of vitamin A. Cancer Res. 33(5): 1003-1009.

Rogers, A.M. and K.C. Back. 1981. Comparative mutagenicity of hydrazine and 3-methylated derivatives in L5178Y mouse lymphoma cells. Mutat. Res. 89(4): 321-328.

Rosenkranz, H.S. and L.A. Poirier. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and non-carcinogens in microbial systems. J. Natl. Cancer Inst. 62(4): 873-892.

Rothberg, S. and O.B. Cope. 1955. Toxicity Studies on Hydrazine, Methylhydrazine, Symmetrical Dimethylhydrazine, Unsymmetrical Dimethylhydrazine and Dimethylnitrosamine (U), Chemical Warfare Laboratories Report No. 2027. Army Chemical Center, Edgewood, MD, U.S. Army Chemical Corps Research and Development Command, Chemical Warfare Laboratories, Toxicology Division, 1955, 21 p. (Summarized in NIOSH, 1978)

Roussel, F., R. Laumonier and J. Tayot. 1980. 1,2-Dimethylhydrazine induced colonic tumors in rats. Biomedicine. 32(1): 41-45.

Rubio, C.A., G. Nylander and M. Santos. 1980. Experimental colon cancer in the absence of intestinal contents in Sprague-Dawley rats. J. Natl. Cancer Inst. 64(3): 569-572.

Schattenkerk, M.E., J.E. Devries, A.K.C. Li, et al. 1981. Decreased dimethylhydrazine-induced colonic neoplasia after submandibular sial adenectomy in male mice. Proc. Am. Assoc. Cancer Res. Am. Soc. Clin. Oncol. 22(0): 106.

Scherfig, J. and P.S. Dixon. 1975. Use of unicellular algae for evaluation of potential aquatic contaminants. Aerosp. Med. Res. Lab. No. AMRL-TR-125. p. 457-491.

Seiler, J.P. 1977. Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens, preliminary results in the validation of a novel short-term test. Mutat. Res. 46: 305-310.

Simmon, V.F. 1979. *In vitro* mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium*. J. Natl. Cancer Inst. 62(4): 893-900.

Simmon, V.F., H.S. Rosenkranz, E. Zieger and L.A. Poirier. 1979. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J. Natl. Cancer Inst. 62(4): 911-918.

Smith, E.B. and D.A. Clark. 1969. The absorption of monomethylhydrazine through canine skin. Proc. Soc. Exp. Biol. Med. 131: 226-232. (Summarized in NIOSH, 1978)

Smith, E.B. and D.A. Clark. 1971. Absorption of unsymmetrical dimethylhydrazine (UDMH) through canine skin. Toxicol. Appl. Pharmacol. 18: 649-659. (Summarized in NIOSH, 1978)

Smith, E.B. and D.A. Clark. 1972. Absorption of hydrazine through canine skin. Toxicol. Appl. Pharmacol. 21: 186-193. (Summarized in NIOSH, 1978)

Stauffer, T.B. 1977. Hydrazine Evaporation. Proc. Conf. Environ. Chem. Hydrazine Fuels, Tyndall AFB, p. 25-38. NTIS AD-A054194.

Sunter, J.P. and P.V. Senior. 1982. Induction of renal tumors in rats by the administration of 1,2-dimethylhydrazine. J. Pathol. 137(1): 63-64.

Suter, W. and I. Jaeger. 1982. Comparative evaluation of different pairs of DNA repair-deficient and DNA repair-proficient bacterial tester strains for rapid detection of chemical mutagens and carcinogens. Mutat. Res. 97: 1-18.

Swenberg, J.A., H.K. Cooper, J. Bucheler and P. Kleihues. 1979. 1,2-Dimethylhydrazine-induced methylation of DNA bases in various rat organs and the effect of pretreatment with disulfiram. Cancer Res. 39(2): 465-467.

Szakal, A.K., B.A. Diwan and K.E. Blackman. 1980. Modulation of immunological competence in 1,2-dimethylhydrazine-sensitive SWR/J mice during colorectal carcinogenesis. Cancer Res. 40(7): 2475-2485.

Tempero, M.A., W. West and R.K. Zetterman. 1981. Failure of dietary cellulose fiber to prevent colon tumors in dimethylhydrazine treated rats on high cholesterol diets. Gastroenterology. 80(5): 1301.

Thurnherr, N., E. Deschner, E.H. Stonehill and M. Lipkin. 1973. Induction of adenocarcinomas of the colon in mice by weekly injections of 1,2-dimethylhydrazine. Cancer Res. 33: 940. (Summarized in IARC, 1973)

Toth, B. 1972. Tumorigenesis studies with 1,2-dimethylhydrazine dihydrochloride, hydrazine sulfate and isonicotinic acid in golden hamsters. Cancer Res. 32: 804.

Toth, B. 1982. Dose-response carcinogenesis by 1,2-dimethylhydrazine dihydrochloride. Fed. Proc. 41(3): 446.

Toth, B. and R.B. Wilson. 1971. Blood vessel tumorigenesis by 1,2-dimethylhydrazine dihydrochloride (symmetrical). Am. J. Pathol. 64: 585.

Trzos, R.J., G.L. Petzold, M.N. Brunden and J.A. Swenberg. 1978. The evaluation of sixteen carcinogens in the rat using the micronucleus test. Mutat. Res. 58(1): 79-86.

Tuazon, E.C., W.P.L. Carter, A.M. Winer and J.N. Pitts, Jr. 1981. Reactions of hydrazines with ozone under simulated atmospheric conditions. Environ. Sci. Technol. 15: 823-828.

Tuazon, E.C., W.P.L. Carter, R.V. Brown, R. Atkinson, A.M. Winer and J.N. Pitts, Jr. 1982. Atmospheric Reaction Mechanisms of Amine Fuels. Report prepared by the Statewide Air Pollution Research Center, University of California, Riverside, CA, for the Air Force Engineering and Services Center, Tyndale AFB, FL. Available from NTIS (AD-A118267).

Turusov, V.S. 1980. Morphology and histogenesis of anal region and clitoral gland tumors induced in mice by 1,2-dimethylhydrazine. J. Natl. Cancer Inst. 64(5): 1161-1167.

Turusov, V.S., N.S. Lanko and Y.D. Parfenov. 1982. Effect of age on induction of intestinal tumors in mice by 1,2-dimethylhydrazine. Oncology 92(12); 1681-1683.

U.S. EPA. 1980. Guidelines and Methodology for the Preparation of Health Effects Assessment Chapters of the Ambient Water Quality Criteria Documents. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH.

Von Wright, A. and L. Tikkanen. 1980. The comparative mutagenicities of hydrazine and its monomethyl and dimethyl derivatives in bacterial test systems. Mutat. Res. 78(1): 17-24.

Weir, F.W., F.H. Myers, R.H. Arbuckle and J.H. Nemenzo. 1965. Further Study of the Acute Toxic Effects of 1,1-Dimethylhydrazine, Methylhydrazine and 1,2-Dimethylhydrazine. U.S. Dept. of Commerce, Springfield, VA. 22 p. NTIS AD 617 692. (Summarized in NIOSH, 1978)

Wilson, R.B. 1976. Species variation in response to dimethylhydrazine. Toxicol. Appl. Pharmacol. 38: 647-650.

Wilson, R.B., D.P. Hutcheson and L. Wideman. 1977. Dimethylhydrazine-induced colon tumors in rats fed diets containing beef fat or corn oil with and without wheat bran. Am. J. Clin. Nutr. 30: 176-181.

Wolter, S. and N. Frank. 1982. Metabolism of 1,2-dimethylhydrazine in isolated perfused rat liver. Chem.-Biol. Interact. 21(3): 335-344.

Zimmerman, F.K. and R. Schwaier. 1967. A genetic effect of symmetric dimethylhydrazine: Induction of mitotic recombination. Naturwissenschaften. 54(10): 251.

APPENDIX A

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values. 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. Documentation of the Threshold Limit Values for Chemical Substances in Work Air. Cincinnati, OH. 94 p.

Bruin, P., G.J. Bergen and J.J. Desta, Ed. 1980. Handling Chemicals Safely. 2nd ed. Dutch Assoc. of Safety Experts, Dutch Chemical Industry Assoc., and Dutch Safety Institute, The Netherlands. 1013 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Muir, G.D., Ed. 1977. Hazards in the Chemical Laboratory, 2nd ed. The London Chemical Society, London. 473 p.

NTP (National Toxicology Program). 1982. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status. Report date: December 31, 1982.

Proctor, N.H. and J. P. Hughes. 1978. Chemical Hazards of the Workplace. J.B. Lippincott Co., Philadelphia. 533 p.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

APPENDIX B

CANCER DATA SHEET FOR DERIVATION OF q_1^*

Compound: 1,2-Dimethylhydrazine

Reference: Toth and Wilson, 1971

Species, Strain, Sex: Mice, Swiss albino, female

Body Weight: 0.03 kg (assumed)

Length of Exposure (l_e) = 371 days (treated), 910 days (controls)

Length of Experiment (L_e) = 371 days (treated), 910 days (controls)

Lifespan of Animal (L) = 910 days

Tumor Site and Type: vascular system/angiosarcoma

Route, Vehicle: oral/drinking water

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding No. Tested (or Examined)
0 mg/day	0	4/110
0.026 mg/day*	0.87	49/50

*0.058 mg/day of 1,2-dimethylhydrazine dihydrochloride was administered; this is the equivalent dose of 1,2-dimethylhydrazine.

Human $q_1^* = 1.38 \times 10^{3}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 7.25×10^{-9} mg/kg/day = 5.08×10^{-7} mg/day for 70 kg man